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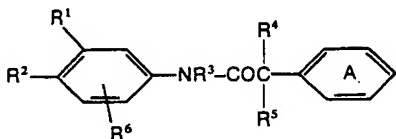
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54. Amide derivatives, process for their manufacture and pharmaceutical or veterinary compositions containing them.

(57) Novel 3,4-disubstituted-N-acylanilines of the formula:

2-p-nitrophenylpropionyl)aniline. Also disclosed are processes for the manufacture of the compounds and pharmaceutical and veterinary compositions containing them.



wherein R¹, R² and ring A are defined in claim 1;
wherein R³ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R⁵ as stated below;

wherein R⁴ is alkyl of 2 to 4 carbon atoms, or has the formula -CX¹X²X³ wherein X¹, X² and X³, which may be the same or different, each is hydrogen, fluorine or chlorine;

wherein R⁵ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R³ to form an oxycarbonyl group such that together with the

-N-CO-C- part of the molecule it forms an oxazolidinedione group; and

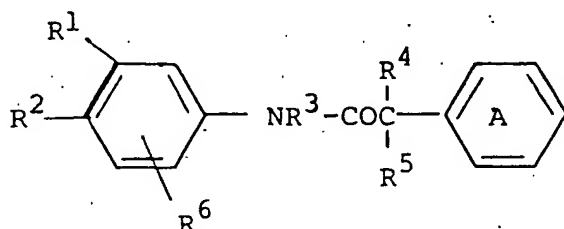
wherein R⁶ is hydrogen or halogen. These compounds possess antiandrogenic activity and are useful for the treatment of androgen dependent or prostatic diseases. Representative of the compounds is 3,4-dichloro-N-(2-hydroxy-

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AMIDE DERIVATIVES, PROCESS FOR THEIR MANUFACTURE
AND PHARMACEUTICAL OR VETERINARY COMPOSITIONS
CONTAINING THEM.

This invention relates to new amide derivatives and more particularly it relates to novel acylanilides which possess antiandrogenic properties.

According to the invention there is provided an acylanilide of the formula:-



wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;

wherein R^3 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;

wherein R^4 is alkyl of 2 to 4 carbon atoms, or has the formula $-CX^1X^2X^3$ wherein X^1 , X^2 and X^3 , which may be the same or different, each is hydrogen, fluorine or chlorine;

wherein R^5 is hydrogen, hydroxy or alkoxy or acyloxy

each of up to 15 carbon atoms, or is joined to R^3 to form an oxycarbonyl group such that together with the $-N-CO-C-$ part of the molecule it forms an oxazolidinedione group;

wherein R^6 is hydrogen or halogen;
and wherein the benzene ring A bears one, two or three
substituents selected from hydrogen, halogen, nitro,
carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl,
5 alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl,
perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoro-
alkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each
of up to 4 carbon atoms, and phenyl, phenylthio, phenyl-
sulphinyl and phenylsulphonyl; or bears a buta-1,3-dienylene
10 substituent which together with the benzene ring A forms
a naphthalene ring.

It will be observed that the acylanilide deriva-
tive of the invention possesses an asymmetric carbon
atom, namely the carbon atom which bears the substituents
15 R^4 and R^5 , and it can therefore exist in racemic and
optically-active forms. It is to be understood that this
invention encompasses the racemic form of the acylanilide
derivative and any optically-active form which possesses
antiandrogenic activity, it being a matter of common
20 general knowledge how a racemic compound may be resolved
into its optically-active forms and how any antiandrogenic
activity present in any of these forms may be determined.

A suitable value for R^1 , R^3 or a substituent
in ring A when it is alkyl is, for example, methyl or
25 ethyl.
 R^3 is preferably hydrogen.

A suitable value for R^1 or a substituent in
ring A when it is alkoxy is, for example, methoxy or
ethoxy.

30 A suitable value for R^1 , R^2 or a substituent
in ring A when it is alkanoyl is, for example, formyl
or acetyl.

A suitable value for R^1 , R^2 or a substituent
in ring A when it is alkylthio, alkylsulphinyl, alkyl-
35 sulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoro-
alkylsulphinyl or perfluoroalkylsulphonyl is, for example,

methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl or trifluoromethylsulphonyl.

A suitable value for R^4 is, for example, methyl, ethyl, n-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl or trichloromethyl. R^4 is preferably methyl.

A suitable value for R^5 when it is alkoxy is, for example, methoxy, ethoxy, propyloxy, n-butyloxy or decyloxy.

A suitable value for R^5 when it is acyloxy is, for example, alkanoyl or aroyl each of up to 15 carbon atoms, for example acetoxy, propionyloxy, decanoyloxy, dodecanoyloxy or benzoyloxy. R^5 is preferably hydroxy.

A suitable value for R^6 or a substituent in ring A when it is halogen is fluoro, chloro, bromo or iodo.

R^6 is preferably hydrogen or chloro, especially hydrogen.

A suitable value for a substituent in ring A when it is alkoxycarbonyl or N-alkylcarbamoyl is, for example, methoxycarbonyl, ethoxycarbonyl or N-methylcarbamoyl.

A preferred combination of values for R^1 and R^2 is as follows:-

R^1	R^2
trifluoromethyl	nitro
trifluoromethyl	cyano
chloro	chloro
chloro	nitro
chloro	cyano
cyano	chloro
nitro	chloro

R ¹	R ²
nitro	cyano
chloro	methylthio
chloro	methylsulphinyl
chloro	methylsulphonyl
methylthio	cyano
hydrogen	methylthio

Ring A preferably contains one or two substituents only, one of which is an electron-withdrawing substituent in the para-position thereof, for example a nitro, fluoro, chloro, trifluoromethyl, cyano, methoxycarbonyl, methylthio, methylsulphinyl or methylsulphonyl substituent; and the other of which is hydrogen or chloro in the meta-position.

In particular, ring A preferably bears a single nitro substituent in the para-position.

A preferred acylanilide of the invention has the formula stated above wherein R¹ and R², which may be the same or different, each is cyano, nitro, trifluoromethyl or chloro, R³ and R⁶ are both hydrogen, R⁴ is methyl, R⁵ is hydroxy and the ring A bears one substituent in the para position which is a nitro, fluoro, trifluoromethyl, cyano, methoxycarbonyl, methylthio or methylsulphinyl substituent.

Specific acylanilides of the invention are hereinafter described in the Examples.

Particularly active compounds are 3,4-dichloro-N-(2-hydroxy-2-p-nitrophenylpropionyl) aniline;
4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline;
4-cyano-3-trifluoromethyl-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline;
3-chloro-4-nitro-N-(2-hydroxy-2-p-nitrophenylpropionyl)-aniline;

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3-chloro-4-methylsulphonyl-N-(2-hydroxy-2-p-nitrophenyl-
propionyl)aniline;

4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-trifluoro-
methylphenylpropionyl)aniline;

5 3-chloro-4-nitro-N-(2-hydroxy-2-p-trifluoromethylphenyl-
propionyl)aniline;

4-nitro-3-trifluoromethyl-N-(2-p-cyanophenyl-2-hydroxy-
propionyl)aniline;

4-nitro-3-trifluoromethyl-N-(2-p-fluorophenyl-2-hydroxy-
10 propionyl)aniline;

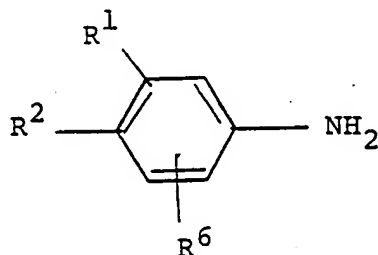
4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methylsulphiny-
phenylpropionyl)aniline;

3,4-dichloro-N-(2-hydroxy-2-p-methylsulphinyphenyl-
propionyl)aniline; and

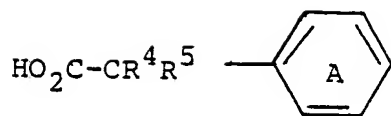
15 3,4-dichloro-N-(2-p-acetylphenyl-2-hydroxypropionyl)-
aniline.

The acylanilides of the invention may be
manufactured by any chemical process known to be
suitable for the manufacture of chemically-analogous
20 compounds.

A preferred process for the manufacture of
an acylanilide of the invention wherein R^3 is hydrogen
and R^5 is other than hydroxy comprises the reaction
of an amine of the formula:-



wherein R^1 , R^2 and R^6 have the meanings stated above,
with an acid of the formula:-

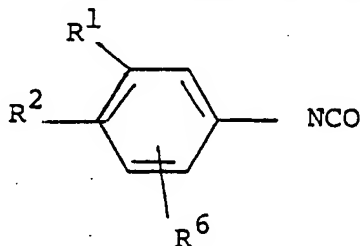


wherein R^4 and A have the meanings stated above and wherein R^5 is hydrogen, alkoxy or acyloxy, or with a reactive derivative of said acid.

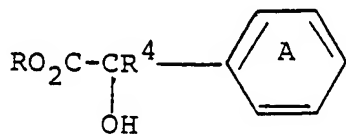
- 5 A suitable reactive derivative of an acid is, for example, an acid anhydride, or an acyl halide, for example an acyl chloride, or a lower alkyl ester of said acid, for example the methyl or ethyl ester. Preferably the reaction is carried out in pyridine
10 solution using an acyl chloride (prepared from the acid and thionyl chloride) as reactant.

The abovementioned process is especially valuable for the manufacture of an acylanilide derivative of the invention wherein R^5 is acyloxy.

- 15 An acylanilide of the invention wherein R^3 and R^5 are joined together to form a carbonyl-oxy group that is, an oxazolidinedione, may be prepared by the reaction of an isocyanate of the formula:-



- 20 wherein R^1 , R^2 and R^6 have the meanings stated above, with an ester of the formula:-



wherein R^4 and A have the meanings stated above and wherein R is alkyl of up to 6 carbon atoms, for example methyl or ethyl. This reaction is preferably carried out in an organic solvent, for example diethyl ether, at laboratory temperature.

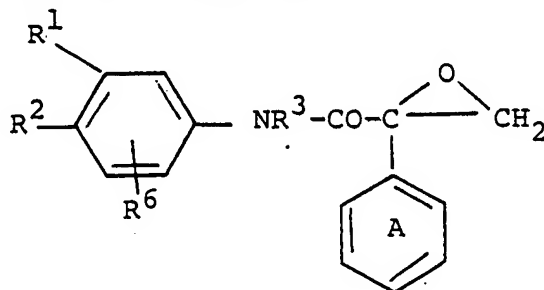
An acylanilide of the invention wherein R^5 is hydroxy may be prepared by the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy, and this is a particularly important method for preparing such compounds when the acylanilide wherein R^5 is acyloxy has been prepared by the preferred process of the invention. An acylanilide of the invention wherein R^5 is hydroxy and R^3 is hydrogen may be prepared by the hydrolysis of the corresponding oxazolidinedione, which may be prepared as described in the preceding paragraph.

An acylanilide of the invention wherein R^3 is alkyl may be prepared by the alkylation of the corresponding acylanilide wherein R^3 is hydrogen.

An acylanilide of the invention wherein R^5 is acyloxy may be prepared by the acylation of the corresponding acylanilide wherein R^5 is hydroxy.

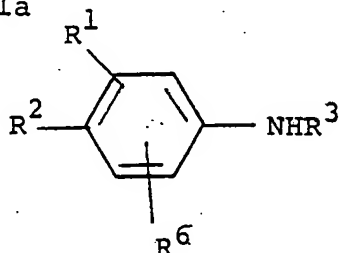
An oxazolidinedione of the invention, wherein R^3 and R^5 are joined together to form a carbonyl-oxy group, may be prepared by the reaction of the corresponding acylanilide wherein R^3 is hydrogen and R^5 is hydroxy with phosgene (COCl_2).

An acylanilide of the invention wherein R^4 is chloromethyl and R^5 is hydroxy may be prepared by the reaction of an epoxide of the formula

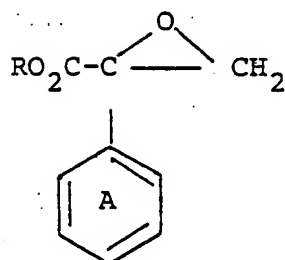


wherein R^1 , R^2 , R^3 , R^6 and A have the meanings stated above, with hydrogen chloride. This reaction is preferably carried out in an organic solvent, for example chloroform, at laboratory temperature.

- 5 The starting material for the last-mentioned reaction may be prepared by the reaction of an aniline of the formula



- 10 wherein R^1 , R^2 , R^3 and R^6 have the meanings stated above, with an epoxide of the formula:-



wherein R and A have the meanings stated above.

- 15 An acylanilide of the invention wherein one or more of R^1 , R^2 and a substituent in the benzene ring A is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, may be prepared by the oxidation of the corresponding acylanilide wherein
- 20 one or more of R^1 , R^2 and a substituent in the benzene ring A is alkylthio, perfluoroalkylthio or phenylthio, respectively. The oxidising agent and conditions used will determine whether a sulphinyl or a sulphonyl compound is obtained. Thus, oxidation with sodium metaperiodate

in methanol solution at or below laboratory temperature will generally convert a thio compound into the corresponding sulphinyl compound; and oxidation with hydrogen peroxide in acetic acid solution at
5 or above laboratory temperature will generally convert a thio compound into the corresponding sulphonyl compound.

An acylanilide of the invention wherein the benzene ring A bears a carboxy substituent
10 may be prepared by the oxidation of the corresponding acylanilide wherein the benzene ring A bears a formyl substituent; and an acylanilide of the invention wherein the benzene ring A bears an alkoxy-carbonyl substituent may be prepared by the ester-
15 ification of the corresponding acylanilide wherein the benzene ring a bears a carboxy substituent.

As stated above, an acylanilide of the invention possesses antiandrogenic properties as demonstrated by its ability to decrease the
20 weight of the seminal vesicles of a mature male rat when administered orally for 4 successive days. An acylanilide of the invention may therefore be used in the treatment of, for example, malignant or benign prostatic disease or of androgen-

dependent disease conditions, such as acne, hirsutism or seborrhoea, in warm-blooded vertebrates including man. It may also be used to improve ovulation in a domestic animal.

5 A preferred acylanilide of the invention is up to 25 times more active as an antiandrogen than the known, chemically-related antiandrogens flutamide and hydroxyflutamide. At a dose of an acylanilide of the invention which produces antiandrogenic activity
10 in rats no symptoms of toxicity are apparent.

 The acylanilide of the invention may be administered to a warm-blooded animal in the form of a pharmaceutical of veterinary composition which comprises the acylanilide in association with a pharmaceutically-
15 acceptable diluent or carrier.

 The composition may be in a form suitable for oral dosage, as a tablet, capsule, aqueous or oily solution or suspension or emulsion. It may alternatively be in the form of a sterile solution or suspension
20 suitable for parenteral administration, or be in the form of an ointment or lotion for topical administration, or be in the form of a suppository.

 The composition may additionally contain one or more drugs selected from anti-oestrogens, for example
25 tamoxifen; progestins, for example medroxyprogesterone acetate; inhibitors of gonadotrophin secretion, for example danazol; cytotoxic agents, for example cyclophosphamide; antibiotics, for example penicillin or oxytetracyclin; and anti-inflammatory agents, for example,
30 especially for topical use, fluocinolone acetonide.

 The acylanilide of the invention will normally be administered to a warm-blooded animal at a dose of between 0.1 mg. and 125 mg. per kg. bodyweight.

 The invention is illustrated but not limited
35 by the following Examples:-

Example 1

Pyridine (0.46 ml.) and thionyl chloride (0.34 ml) were added to a solution of 2-acetoxy-2-p-nitrophenylpropionic acid (1.23 g.) in methylene chloride (20 ml.) and the mixture was stirred at laboratory temperature for 30 minutes and then evaporated to dryness under reduced pressure. The residue was dissolved in pyridine (25 ml.), 3,4-dichloro-aniline (0.78 g.) was added and the mixture was stirred for 17 hours and then evaporated to dryness. The residue was partitioned between ethyl acetate and dilute aqueous hydrochloric acid, and the ethyl acetate solution was separated, washed successively with dilute aqueous hydrochloric acid, water, aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, then dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was crystallised from toluene and there was thus obtained 3,4-dichloro-N-(2-acetoxy-2-p-nitrophenylpropionyl)-aniline, m.p. 135-136°C.

This product (1.0 g) was dissolved in a 20:1 v/v mixture of ethanol and tetrahydrofuran (25 ml.), 5% aqueous potassium hydroxide solution (5 ml.) was added and the mixture was allowed to stand for 10 minutes and was then evaporated to dryness. The residue was partitioned between ethyl acetate and saturated aqueous sodium chloride solution, and the ethyl acetate solution was separated, dried over magnesium sulphate and evaporated to dryness. The residue was crystallised from toluene and there was thus obtained 3,4-dichloro-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline, m.p. 179-180°C.

The 2-acetoxy-2-p-nitrophenylpropionic acid used as starting material was obtained as follows:-

Zinc iodide (0.05 g.) and trimethylsilyl cyanide (36 g.) were added to a stirred solution of p-nitroacetophenone (50 g.) in methylene dichloride (500 ml.) and the mixture was stirred at laboratory temperature for 48 hours and then evaporated to dryness under reduced pressure. Aqueous 3N-hydrochloric acid (500 ml.) was added and the mixture was heated at 50°C. for 5 hours, cooled and poured into water. The mixture was extracted three times with ethyl acetate and the combined extracts were washed with water and then with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. A mixture of the 2-hydroxy-2-p-nitrophenylpropionitrile thus obtained (1.2 g.) and concentrated aqueous hydrochloric acid (20 ml.) was heated for 4 hours at 110°C. in a sealed tube. The mixture was diluted with water and extracted with ethyl acetate, and the ethyl acetate extract was washed successively with water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. A mixture of the 2-hydroxy-2-p-nitrophenylpropionic acid thus obtained (1.3 g.), acetic anhydride (1.25 ml.) and pyridine (20 ml.) was stirred at laboratory temperature for 17 hours and then evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and dilute aqueous hydrochloric acid and the ethyl acetate solution was separated, washed successively with dilute aqueous hydrochloric acid, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. There was thus obtained as solid residue 2-acetoxy-2-p-nitrophenylpropionic acid which was used without further purification.

Example 2

The process described in the first and second paragraph of Example 1 was repeated except that the appropriate aniline and the appropriate 2-acetoxy-2-

phenylalkanoic acid were used as starting materials. There were thus obtained the compounds described in the following table:-

R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
Cl	Cl	CH ₃	-	127-128
Cl	Cl	CH ₃	3-NO ₂	150-151
Cl	Cl	CH ₃	3-NO ₂ -4-Cl	120-122
Cl	Cl	CH ₃	3-CF ₃	118-119
Cl	Cl	CH ₃	4-Cl	143-145
Cl	Cl	CF ₃	-	118-119
Cl	Cl	CF ₃	3-CH ₃ O	(gum)
CF ₃	NO ₂	CH ₃	-	116-117
CF ₃	NO ₂	CH ₃	4-NO ₂	126-127
CF ₃	NO ₂	CH ₃	3-NO ₂	175-176
CF ₃	NO ₂	CH ₃	3-NO ₂ -4-Cl	122-123
CF ₃	NO ₂	CH ₃	2-NO ₂	180-181
CF ₃	NO ₂	CH ₃	4-CF ₃	137-143

Continued....

R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
CF ₃	NO ₂	CH ₃	3-CF ₃	120-121
CF ₃	NO ₂	CH ₃	4-Cl	108-109
CF ₃	NO ₂	CH ₃	3-Cl	133-134
CF ₃	NO ₂	CH ₃	3,4-diCl	146-147
CF ₃	NO ₂	CF ₃	-	134-136
CF ₃	NO ₂	CF ₃	4-Cl	131-132
CF ₃	NO ₂	CF ₃	4-CH ₃	147-148
CF ₃	CN	CH ₃	4-NO ₂	186-188
CH ₃ O	CN	CH ₃	4-NO ₂	155-156
NO ₂	Cl	CH ₃	4-NO ₂	160-162

Example 3

The process described in the first and second paragraphs of Example 1 was repeated except
 5 that the appropriate aniline and the appropriate 2-acetoxy-2-phenylalkanoic acid were used as starting materials. There were thus obtained the compounds described in the following table:-

R^1	R^2	R^4	Ring A Substituent	m.p. ($^{\circ}\text{C}$).
Cl	Cl	CH_3	4- CF_3	130-131
Cl	Cl	CH_3	4-F	131-132
Cl	Cl	CH_3	4-CN	159-161
Cl	Cl	CH_3	4- C_6H_5	135-136
Cl	Cl	CH_3	4-CHO	137-138
Cl	Cl	CH_3	4- COCH_3	(gum)
Cl	Cl	CH_3	4- SC_6H_5	(gum)
Cl	Cl	CH_3	4- SCH_3	154-157
CF_3	NO_2	CH_3	4- NO_2	128-130
CF_3	NO_2	CH_3	4- NO_2	(-)-isomer 139-140
CF_3	NO_2	CH_3	4-F	(+)-isomer 107-108
CF_3	NO_2	CH_3	4-CN	125-130
CF_3	NO_2	CH_3	4- C_6H_5	168-169
CF_3	NO_2	CH_3	(1-naphthyl)	182-185
CF_3	NO_2	CH_3	(2-naphthyl)	111-113

Continued....

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R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
CF ₃	NO ₂	CH ₃	4-CHO	55-57
CF ₃	NO ₂	CH ₃	4-COCH ₃	133-134
CF ₃	NO ₂	CH ₃	4-SCH ₃	118-122
CF ₃	NO ₂	CH ₃	4-SC ₆ H ₅	(gum)
CF ₃	CN	CH ₃	4-CF ₃	191-192
CF ₃	F	CH ₃	4-NO ₂	120-122
CF ₃	Br	CH ₃	4-NO ₂	139-140
Cl	COCH ₃	CH ₃	4-NO ₂	136-139
Cl	CH ₃ S	CH ₃	4-NO ₂	153-154
Cl	CH ₃ S	CH ₃	4-CF ₃	(gum)
Cl	CH ₃ S	CH ₃	4-CN	(gum)
Cl	NO ₂	CH ₃	4-NO ₂	179-180
Cl	NO ₂	CH ₃	4-CF ₃	161-162
Cl	NO ₂	CH ₃	4-F	123-124
Cl	NO ₂	CH ₃	4-CN	152-154
Cl	NO ₂	CH ₃	4-COCH ₃	58

Continued....

R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
Cl	NO ₂	CH ₃	4-SCH ₃	(gum)
Cl	CN	CH ₃	4-NO ₂	189-190
Cl	CN	CH ₃	4-CF ₃	202-203
Cl	CN	CH ₃	4-F	132-133
Cl	CN	CH ₃	4-CN	96-98
Cl	CN	CH ₃	4-CHO	79-81
Cl	CN	CH ₃	4-COCH ₃	64-67
Cl	CN	CH ₃	4-SCH ₃	(gum)
Cl	CN	CH ₃	4-SC ₆ H ₅	(gum)
CN	Cl	CH ₃	4-NO ₂	156-157
NO ₂	Cl	CH ₃	4-CF ₃	118-120
NO ₂	CN	CH ₃	4-NO ₂	92-93
NO ₂	CN	CH ₃	4-SCH ₃	(gum)
NO ₂	CN	CH ₃	4-CF ₃	167-169

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R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
NO ₂	CN	CH ₃	4-CN	115-118
CH ₃ S	CN	CH ₃	4-NO ₂	148-149
CH ₃ S	CN	CH ₃	4-CF ₃	(gum)
CH ₃ S	CN	CH ₃	4-SCH ₃	(gum)
CH ₃	CN	CH ₃	4-NO ₂	171-172
CH ₃ O	CN	CH ₃	4-CF ₃	165-167
NO ₂	Cl	CH ₃	4-CN	129-134
H ₂ NCO	Cl	CH ₃	4-NO ₂	208-210
H	CF ₃	CH ₃	4-NO ₂	153-154
H	CF ₃ S	CH ₃	4-NO ₂	164-165
H	CH ₃ S	CH ₃	4-NO ₂	161-162
C ₆ H ₅ S	NO ₂	CH ₃	4-NO ₂	(gum)
CF ₃	NO ₂	CF ₃	3-CH ₃	165-166
Cl	Cl	CF ₃	4-Cl	135
CF ₃	NO ₂	C ₂ H ₅	-	125-128
CF ₃	NO ₂	n-C ₃ H ₇	-	107-108
Cl	Cl	n-C ₃ H ₇	-	85-86

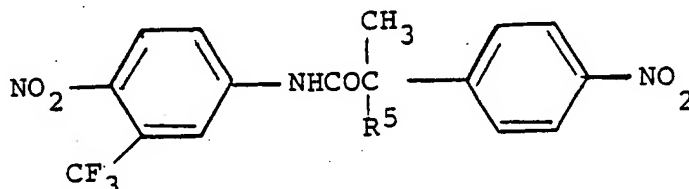
Continued...

R ¹	R ²	R ⁴	Ring A Substituent	m.p. (°C.)
Cl	Cl	CHF ₂	4-SCH ₃	(gum)
Cl	Cl	CHCl ₂	4-SCH ₃	(gum)
Cl	CN	CHCl ₂	4-SCH ₃	(gum)
Cl	Cl	CH ₂ F	-	115-116

There were also similarly prepared 3,4,5-trichloro-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline, m.p. 232-235°C. and 2-chloro-4-nitro-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline, m.p. 155-157°C.

Example 4

The process described in the first part of Example 1 was repeated except that 4-nitro-3-trifluoromethylaniline and the appropriate 2-acyloxy-2-p-nitro-phenylpropionic acid were used as starting materials. There were thus obtained the compounds described in the following table:



R ⁵	m.p. (°C.)
acetoxy	163-164
benzoyloxy	98-100
n-dodecanoyloxy	50-70

PREPARATION OF STARTING MATERIALS

The 2-acyloxy-2-phenylalkanoic acids used as starting materials in Examples 2, 3 and 4 were obtained from the corresponding 2-hydroxy-2-phenylalkanoic acids by a similar process to that described in the final part of Example 1. The 2-hydroxy-2-phenylalkanoic acids themselves were obtained either

(a) from the corresponding alkanophenone by a similar process to that described in the final part of Example 1, or

(b) by the reaction of an aryl-metallo compound with an α-ketoacid as exemplified by the following preparation of 2-p-fluorophenyl-2-hydroxypropionic acid:-

A Grignard reagent was prepared from a solution of 1-bromo-4-fluorobenzene (50 g.) in diethyl ether (100 ml.) and a stirred suspension of magnesium (6.8 g.)

- 21 -

in diethyl ether (20 ml.), and was heated under reflux for 1 hour and then cooled to 0°C. A solution of pyruvic acid (10.8 g.) in diethyl ether (50 ml.) was added dropwise and the mixture was
5 stirred at laboratory temperature for 17 hours, cooled to 0°C., acidified with dilute aqueous hydrochloric acid and extracted three times with diethyl ether. The combined ethereal extracts were washed with water and extracted with saturated aqueous sodium bicarbonate
10 solution, and the bicarbonate extract was acidified with concentrated aqueous hydrochloric acid and then extracted three times with ethyl acetate. The combined ethyl acetate extracts were washed with water and then with saturated aqueous sodium chloride solution, dried
15 over magnesium sulphate and evaporated to dryness under reduced pressure. There was thus obtained as residue 2-p-fluorophenyl-2-hydroxypropionic acid which was used without further purification.

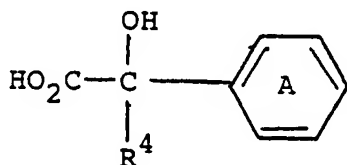
Process (b) described above was used to prepare
20 2-aryl-2-hydroxypropionic acids wherein the 2-aryl group was:

3-chlorophenyl	4-methylthiophenyl
4-chlorophenyl	4-phenylthiophenyl
3-trifluoromethylphenyl	1-naphthyl
4-trifluoromethylphenyl	2-naphthyl

Process (b) described above was also used to prepare 2-p-diethoxymethylphenyl- and 2-p-(1,1-diethoxyethyl)-phenyl-2-hydroxypropionic acid, which were hydrolysed to 2-p-formylphenyl- and 2-p-acetylphenyl-2-hydroxypropionic acid respectively by heating under reflux for 17 hours in dioxan solution with aqueous 2N-sulphuric acid.

2-p-Cyanophenyl-2-hydroxypropionic acid was prepared by a similar process to process (b) except that the organolithium compound prepared from a solution of 4-bromobenzonitrile (2 g.) in tetrahydrofuran (100 ml.) and n-butyl-lithium (7.3 ml of a 1.5 molar solution in hexane) at -90°C . was added to a solution of ethyl pyruvate (1.2 ml.) in tetrahydrofuran (100 ml.) at -100°C ., the reaction mixture was worked up in conventional manner, and the ethyl ester was hydrolysed to the acid by conventional means.

Process (a) described above was used to prepare the following acids of the formula:-



R ⁴	Ring A Substituent	R ⁴	Ring A Substituent
CH ₃	2-NO ₂	CF ₃	4-Cl
CH ₃	3-NO ₂	CF ₃	3-CH ₃ O
CH ₃	3,4-diCl	CF ₃	4-CH ₃
CH ₃	3-NO ₂ -4-Cl	CF ₃	3-CH ₃
CHF ₂	4-CH ₃ S	CF ₃	—
CHCl ₂	4-CH ₃ S	CH ₂ F	—

2-Hydroxy-2-phenylpropionic, butyric and valeric acids, and 2-hydroxy-2-(4-biphenyl)propionic acid are known compounds.

All the alkanophenones used as starting materials in process (a) are known compounds apart from 4-methylthio- α,α -difluoroacetophenone which was prepared as follows:-

n-Butyl-lithium (3.25 ml. of a 1.6 molar solution) was added dropwise to a stirred solution of 1-bromo-4-methylthiobenzene (1.06 g.) in tetrahydrofuran (50 ml.) which was maintained at $-78^{\circ}\text{C}.$, and the mixture was stirred at that temperature for 1 hour and then added to a solution of difluoroacetic acid (0.25 g.) in tetrahydrofuran (30 ml.). The mixture was stirred at $-78^{\circ}\text{C}.$ for 2 hours, acetic acid (0.5 ml.) was added and the mixture was allowed to warm up to room temperature and was then poured into water. The organic layer was separated, washed successively with saturated aqueous sodium bicarbonate solution, water and saturated sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue consisted of 4-methylthio- α,α -difluoroacetophenone and was used without further purification.

All the anilines used as starting materials in Examples 2, 3 and 4 are known compounds apart from 4-cyano-3-methylthioaniline, which was prepared as follows:-

A stirred mixture of 2-chloro-4-nitrobenzoic acid (12.1 g.) , dimethyldisulphide (2.8 ml.), copper powder (3.8 g.) and N,N-dimethylacetamide (80 ml.) was heated to $135^{\circ}\text{C}.$ during 1 hour, kept at that temperature for 90 minutes, and then heated at $165^{\circ}\text{C}.$ for 2 hours.

The N,N-dimethylacetamide was removed by distillation under reduced pressure and the residue was poured into a mixture of water (400 ml.) and 32% w/v aqueous sodium hydroxide solution (10 ml.). The mixture was filtered and the filtrate was washed with ethyl acetate, acidified with concentrated aqueous hydrochloric acid and filtered.

The solid residue was washed with water and then dissolved in ethyl acetate, and the solution was dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was crystallised from aqueous ethanol
5 and there was thus obtained 2-methylthio-4-nitrobenzoic acid, m.p. 214-215°C.

Thionyl chloride (29 ml.) was added to a stirred suspension of the above compound (42.6g.) in petroleum ether, b.p. 60-80°C. (800 ml.) containing
10 piperidine (0.1 ml.) and the mixture was heated under reflux for 150 minutes and then evaporated to dryness under reduced pressure. A solution of the residue in tetrahydrofuran (100 ml.) was added to a stirred mixture of aqueous ammonium hydroxide solution (190 ml., specific
15 gravity 0.88) and ice (250 g.) and the mixture was stirred at laboratory temperature for 16 hours, acidified with concentrated aqueous hydrochloric acid and filtered. The solid residue was washed with ice-cold water, and then stirred with saturated aqueous sodium bicarbonate solution,
20 and the mixture was filtered. There was thus obtained as solid residue 2-methylthio-4-nitrobenzamide, m.p. 202-204°C.

Trifluoroacetic anhydride (25.8 ml.) was added to a cooled, stirred suspension of the above compound
25 (35.25 g.) in a mixture of dioxane (400 ml.) and pyridine (28 ml.) at such a rate that the temperature of the mixture was maintained at 10-12°C, and the mixture was then stirred at laboratory temperature for 15 hours and poured into ice-water (3 litres). The mixture was filtered
30 and the solid residue was crystallised from ethanol. There was thus obtained 2-methylthio-4-nitrobenzonitrile, m.p. 180-181°C.

The above compound (30 g.) was added in portions during 50 minutes to a stirred mixture of water (800 ml.), ethanol (200 ml.), glacial acetic acid (60 ml.) and iron powder (150 g.) which was heated at 85-90°C, and
5 the mixture was stirred at this temperature for a further 3 hours and then basified to pH 9 with aqueous sodium hydroxide solution. The mixture was shaken with diethyl ether (200 ml.) and the whole mixture filtered through a filter-aid. The solid residue was washed with diethyl
10 ether (400 ml) and the aqueous part of the filtrate was extracted five times with diethyl ether (100 ml. each time). The combined ethereal solutions were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue consisted
15 of 4-cyano-3-methylthioaniline, m.p. 105-107.5°C.

Example 5

A mixture of 2-methoxy-2-p-nitrophenylpropionic acid (0.3 g.) and thionyl chloride (3 ml.) was heated under reflux for 1 hour, evaporated to dryness under reduced pressure and the residue was dissolved in pyridine (15 ml.). 4-Nitro-3-trifluoromethylaniline (0.25 g.) was added and the mixture was stirred at laboratory temperature for 17 hours and then evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and dilute aqueous hydrochloric acid and the ethyl acetate layer was washed successively with water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, then dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (20 g.) using a 4:1 v/v mixture of toluene and ethyl acetate as eluant, and the product obtained was crystallised from toluene. There was thus obtained N-(2-methoxy-2-p-nitrophenylpropionyl)-4-nitro-3-trifluoromethylaniline, m.p. 151-153°C.

The 2-methoxy-2-p-nitrophenylpropionic acid used as starting material was obtained as follows:-

A mixture of 2-hydroxy-2-p-nitrophenylpropionic acid (0.7 g.; last paragraph of Example 1), concentrated sulphuric acid (0.5 ml.) and methanol (30 ml.) was heated under reflux for 3 hours, evaporated to dryness under reduced pressure and the residue was partitioned between ethyl acetate and water. The ethyl acetate layer was washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residual methyl 2-hydroxy-2-p-nitrophenylpropionate (0.45 g.) was added to a stirred mixture of potassium

hydroxide (0.45 g.) and dimethyl sulphoxide (2 ml.) which had been stirred for 5 minutes under an atmosphere of argon, methyl iodide (0.56 g.) was added immediately and the mixture was stirred for 2 hours at laboratory
5 temperature under an atmosphere of argon. Water (5 ml.) was then added and the mixture was extracted with ethyl acetate. The extract was washed with water and then with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under
10 reduced pressure. A mixture of the residue, ethanol (5 ml.) and aqueous 2N-sodium hydroxide solution (0.76 ml.) was heated under reflux for 1 hour, stirred at laboratory temperature for 17 hours and then evaporated to dryness under reduced pressure. The residue was
15 partitioned between ethyl acetate and dilute aqueous hydrochloric acid. The ethyl acetate layer was washed with water, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue consisted of 2-methyl-2-p-nitrophenylpropionic acid and was used
20 without further purification.

The process described above was repeated using 2-n-butoxy-2-p-nitrophenylpropionic acid (prepared as described in the second paragraph above except that n-butyl iodide was used in place of methyl iodide) as
25 starting material. There was thus obtained N-(2-n-butoxy-2-p-nitrophenylpropionyl)-4-nitro-3-trifluoromethylaniline, m.p. 124-127°C.

Example 6

A mixture of 2-p-nitrophenylpropionic acid (2.4g.), methylene chloride (40ml.), pyridine (0.98ml.) and thionyl chloride (0.83ml.) was stirred at laboratory temperature for 1 hour and then evaporated to dryness under reduced pressure. The residue was dissolved in pyridine (50ml.), 4-nitro-3-trifluoromethylaniline (2.5g.) was added and the mixture was stirred at laboratory temperature for 17 hours and then evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and dilute aqueous hydrochloric acid and the ethyl acetate layer was washed successively with dilute aqueous hydrochloric acid, water, saturated aqueous sodium bicarbonate solution and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (120g.) using a 3:2 v/v mixture of chloroform and ethyl acetate as eluant, and the product was crystallised from toluene. There was thus obtained 4-nitro-3-trifluoromethyl-N-(2-p-nitrophenylpropionyl)aniline, m.p. 161-162°C.

The 2-p-nitrophenylpropionic acid used as starting material was obtained as follows:

Diethyl malonate (11g.) was added dropwise to a stirred mixture of sodium hydride (3g. of a 50% dispersion in mineral oil from which the oil has been removed by washing with petroleum ether) and dimethylformamide (150ml.) and the mixture was stirred at laboratory temperature for 1 hour. A solution of 4-nitrochlorobenzene (10g.) in dimethylformamide (15ml.) was added dropwise, and the mixture was then heated at 100°C. for 17 hours, cooled and evaporated to dryness under reduced pressure. The residue was partitioned

between ethyl acetate and water and the ethyl acetate layer was washed with water and then with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure.

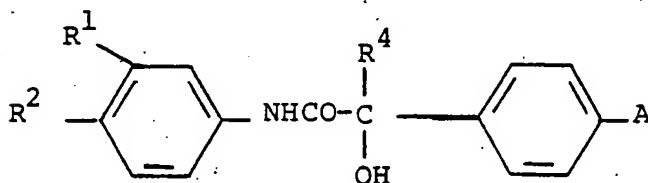
5 The residue was distilled and there was thus obtained diethyl 2-methyl-2-p-nitrophenylmalonate, b.p. 143-145°C./0.15mm.Hg.

A mixture of the above compound (4.0g.), aqueous 2N-sodium hydroxide solution (20ml.) and ethanol
10 (100ml.) was stirred at laboratory temperature for 17 hours and then evaporated to dryness under reduced pressure. To the residue were added water (80ml.) and concentrated aqueous hydrochloric acid (20ml.) and the mixture was heated at 100°C. for 6 hours, cooled and extracted 3 times
15 with ethyl acetate. The combined extracts were themselves extracted 3 times with saturated aqueous bicarbonate solution and the combined extracts were acidified with concentrated aqueous hydrochloric acid and extracted three times with ethyl acetate. The combined extracts were
20 washed with water and then with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue consisted of 2-p-nitrophenylpropionic acid and was used without further purification.

Example 7

A solution of sodium metaperiodate (0.79 g.) in water (14.7 ml.) was added dropwise to a stirred solution of 4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methylthiophenylpropionyl) aniline (Example 3; 1.4 g.) in methanol (35 ml.) which was maintained at 0°C. The mixture was allowed to warm up to laboratory temperature and was then stirred for 17 hours. Saturated aqueous sodium chloride solution (50 ml.) was added and the mixture was extracted twice with ethyl acetate (50 ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness. The residue was crystallised from a mixture of ethyl acetate and petroleum ether (b.p. 60-80°C.) and there was thus obtained 4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methanesulphonylphenylpropionyl) aniline, m.p. 171-175°C.

The process described above was repeated using the appropriate anilide bearing an alkylthio or arylthio substituent and there were thus obtained the compounds described in the following table:-



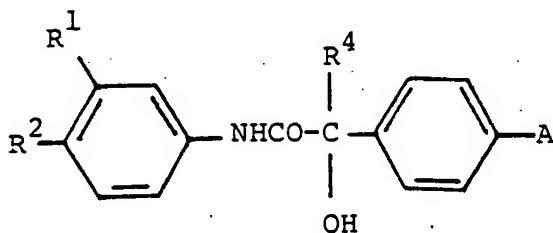
R ¹	R ²	R ⁴	A	m.p. (°C.)
Cl	Cl	CH ₃	SOCH ₃	170-181
Cl	Cl	CH ₃	SOC ₆ H ₅	179-181
CF ₃	NO ₂	CH ₃	SOC ₆ H ₅	156-158
Cl	CN	CH ₃	SOCH ₃	110-111
Cl	CN	CH ₃	SOC ₆ H ₅	195-197
Cl	NO ₂	CH ₃	SOCH ₃	179-180
NO ₂	CN	CH ₃	SOCH ₃	226-227
Cl	SOCH ₃	CH ₃	NO ₂	253-254
Cl	SOCH ₃	CH ₃	CN	148-155
H	SOCH ₃	CH ₃	NO ₂	138-139
H	SOCF ₃	CH ₃	NO ₂	143-144 *
SOCH ₃	CN	CH ₃	NO ₂	125-128
SOCH ₃	CN	CH ₃	CF ₃	164-166
SOCH ₃	CN	CH ₃	SOCH ₃	234-238
Cl	CN	CHCl ₂	SOCH ₃	(gum)

* Oxidation carried out with m-chloroperbenzoic acid in methylene dichloride solution.

Example 8

A mixture of 4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methylthiophenylpropionyl)aniline (1.1g.), glacial acetic acid (37ml.) and hydrogen peroxide (2.8ml., 100 vols.) was stirred at 70°C. for 5 hours, cooled, diluted with water (25ml.) and extracted 3 times with ethyl acetate (25ml. each time). The combined extracts were washed with saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was crystallised from a mixture of ethyl acetate and toluene and there was thus obtained 4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methanesulphonylphenylpropionyl)aniline, m.p. 187-189°C.

The process described above was repeated using the appropriate anilide bearing an alkylthio or arylthio substituent, and there were thus obtained the compounds described in the following table:-



R ¹	R ²	R ⁴	A	m.p. (°C.)
Cl	Cl	CH ₃	SO ₂ CH ₃	212-215
CF ₃	NO ₂	CH ₃	SO ₂ C ₆ H ₅	79-82
Cl	SO ₂ CH ₃	CH ₃	NO ₂	200-201
Cl	SO ₂ CH ₃	CH ₃	CN	175-176
Cl	SO ₂ CH ₃	CH ₃	CF ₃	133-134
H	SO ₂ CH ₃	CH ₃	NO ₂	200-201
H	SO ₂ CF ₃	CH ₃	NO ₂	181-182

Continued..

R^1	R^2	R^4	A	m.p. ($^{\circ}\text{C.}$)
$\text{SO}_2\text{C}_6\text{H}_5$	NO_2	CH_3	NO_2	Not (Crystalline)
Cl	Cl	CHCl_2	SO_2CH_3	102-103
Cl	Cl	CHF_2	SO_2CH_3	168-170
SO_2CH_3	CN	CH_3	NO_2	249-251*

* Oxidation carried out at laboratory temperature.

Example 9

Aqueous 2N-sodium hydroxide solution (1.12 ml.) was added to a solution of methyl 2,3-epoxy-2-p-nitrophenylpropionate (0.5 g.) in a mixture of ethanol (15 ml.), tetrahydrofuran (3 ml.) and water (3 ml.) and the mixture was stirred at laboratory temperature for 1 hour and then evaporated to dryness under reduced pressure. The residue was suspended in toluene (20 ml.), oxalyl chloride (0.25 ml.) was added and the mixture was stirred at laboratory temperature for 2 hours. Pyridine (10 ml.) and 4-nitro-3-trifluoromethylaniline (0.462 g.) were added and the mixture was stirred at laboratory temperature for 2 hours and then evaporated to dryness under reduced pressure. The residue was partitioned between ethyl acetate and dilute aqueous hydrochloric acid and the ethyl acetate layer was washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residual gum was dissolved in chloroform (50 ml.), the solution was saturated with hydrogen chloride and the mixture was stirred for 17 hours at laboratory temperature and then poured into water. The mixture was extracted three times with diethyl ether and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The residue was purified by chromatography on a silica gel column (20 g.) using a 2:3 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80°C.) as eluant, and the product was crystallised from toluene. There was thus obtained 4-nitro-3-trifluoromethyl-N-(3-chloro-2-hydroxy-2-p-nitrophenylpropionyl)aniline, m.p. 154-157°C.

The methyl 2,3-epoxy-2-p-nitrophenylpropionate used as starting material was obtained as follows:

Benzonitrile (1 ml.), potassium carbonate (0.2 g.) and 30% aqueous hydrogen peroxide solution (1.5 ml.) were added to a solution of methyl 2-p-nitrophenylprop-2-enoate (1.0 g.) in a mixture of methanol (15 ml.) and chloroform (15 ml.) and the mixture was stirred at laboratory temperature for 17 hours and then poured into water. The mixture was extracted three times with diethyl ether and the combined extracts were washed successively with water, aqueous ferrous sulphate solution and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. There was thus obtained as solid residue methyl 2,3-epoxy-2-p-nitrophenylpropionate which was used without further purification.

15 The process described above was repeated using the appropriate aniline in place of 4-nitro-3-trifluoromethylaniline, and there were thus obtained 3,4-dichloro-N-(3-chloro-2-hydroxy-2-nitrophenylpropionyl) aniline, m.p. 78-82°C., and 3-chloro-4-cyano-N-(3-chloro-2-hydroxy-2-p-nitrophenylpropionyl) aniline, m.p. 186-189°C.

Example 10

Jones' reagent (a 25% w/w solution of chromium trioxide in sulphuric acid) was added to a solution of 3,4-dichloro-N-(2-p-formylphenyl-2-hydroxypropionyl)-aniline (Example 3; 1.0 g.) in acetone (50 ml.) until a permanent yellow colour persisted, and the mixture was then filtered. The filtrate was evaporated to dryness under reduced pressure, the residue was dissolved in methanol (20 ml.), concentrated sulphuric acid (0.5 ml.) was added and the mixture was heated under reflux for 3 hours, cooled and poured into water. The mixture was extracted three times with diethyl ether and the combined extracts were washed successively with saturated aqueous sodium bicarbonate solution, water and saturated aqueous sodium chloride solution, dried over magnesium sulphate and evaporated to dryness under reduced pressure. The product was purified by chromatography on a silica gel column using a 1:1 v/v mixture of ethyl acetate and petroleum ether (b.p. 60-80°C). There was thus obtained 3,4-dichloro-N-(2-hydroxy-2-p-methoxycarbonyl-phenylpropionyl)aniline, m.p. 109°C.

The process described above was repeated using the appropriate p-formylphenyl compound, and there were thus obtained the compounds described in the following table:-

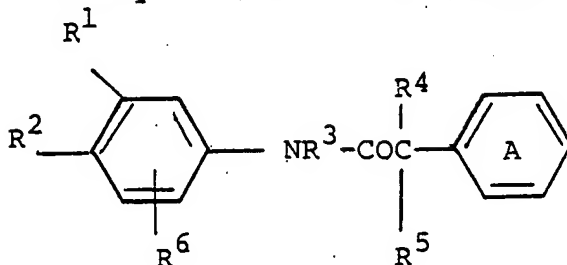
R ¹	R ²	m.p. (°C.)
CF ₃	NO ₂	87-88
Cl	CN	103-106

Example 11

A solution of 4-nitro-3-trifluoromethylphenyl isocyanate (1.5 g.) in diethyl ether (30 ml.) was added dropwise to a stirred solution of methyl 2-hydroxy-
5 2-p-nitrophenylpropionate (1.0 g.) and 1,3-diamino propane (0.1 g.) in diethyl ether (20 ml.), and the mixture was stirred at laboratory temperature for 65 hours and then filtered. The solid residue was crystallised from a mixture of toluene and petroleum
10 ether (b.p. 60-80°C.) and there was thus obtained 5-methyl-5-p-nitrophenyl-3-(4-nitro-3-trifluoromethyl-phenyl)oxazolidine-2,4-dione, m.p. 175-177°C.

What we claim is:-

1. An acylanilide of the formula:-



- wherein R¹ is cyano, carbamoyl, nitro, fluoro, chloro,
 5 bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
 10 wherein R² is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms, or phenylthio, phenylsulphinyl
 15 or phenylsulphonyl;
 wherein R³ is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R⁵ as stated below;
 wherein R⁴ is alkyl of 2 to 4 carbon atoms, or has the formula -CX¹X²X³ wherein X¹, X² and X³, which may be the
 20 same or different, each is hydrogen, fluorine or chlorine;
 wherein R⁵ is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R³ to form an oxycarbonyl group such that together with the
 25 -N-CO-C- part of the molecule it forms an oxazolidine-dione group;
 wherein R⁶ is hydrogen or halogen;
 and wherein the benzene ring A bears one, two or three substituents selected from hydrogen, halogen, nitro,

carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphanyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphanyl, perfluoroalkylsulphonyl, alkoxycarbonyl and N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphanyl and phenylsulphonyl;

or bears a buta-1,3-dienylene substituent which together with the benzene ring A forms a naphthelene ring.

2. An acylanilide as claimed in claim 1 wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo, hydrogen, methyl, ethyl, methoxy, ethoxy, formyl, acetyl, methylthio, ethylthio, methylsulphanyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphanyl, trifluoromethylsulphonyl, phenylthio, phenylsulphanyl or phenylsulphonyl;

wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo, formyl, acetyl, methylthio, ethylthio, methylsulphanyl, methylsulphonyl, trifluoromethyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphanyl, trifluoromethylsulphonyl, phenylthio, phenylsulphanyl or phenylsulphonyl;

wherein R^3 is hydrogen, methyl or ethyl, or is joined to R^5 as stated below;

wherein R^4 is methyl, ethyl, n-propyl, fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl or trichloromethyl;

wherein R^5 is hydrogen, hydroxy, methoxy, ethoxy, propyloxy, n-butyloxy, decyloxy, acetoxy, propionyloxy, decanoyloxy or dodecanoyloxy, or is joined to R^3 to form an oxycarbonyl group as stated in claim 1;

wherein R^6 is hydrogen or chloro;

and wherein the benzene ring A bears one or two

substituents selected from hydrogen, fluoro, chloro, bromo, iodo, nitro, carboxy, carbamoyl, cyano, methyl, ethyl, methoxy, ethoxy, formyl, acetyl, methylthio, ethylthio, methylsulphinyl, methylsulphonyl, trifluoro-
 5 methyl, pentafluoroethyl, trifluoromethylthio, trifluoromethylsulphinyl, trifluoromethylsulphonyl, methoxycarbonyl, ethoxycarbonyl, N-methylcarbamoyl, phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or bears a 1,3-butadienylene substituent as stated in
 10 claim 1.

3. An acylanilide as claimed in claim 1 wherein R^1 is trifluoromethyl and R^2 is nitro or cyano; or R^1 is chloro and R^2 is chloro, nitro, cyano, methylthio, methylsulphinyl or methylsulphonyl; or
 15 R^1 is cyano and R^2 is chloro; or R^1 is nitro and R^2 is chloro or cyano; or R^1 is methylthio and R^2 is cyano; or R^1 is hydrogen and R^2 is methylthio; wherein R^3 is hydrogen;
 20 wherein R^4 is methyl; wherein R^5 is hydroxy; wherein R^6 is hydrogen;

and wherein the benzene ring A bears one or two substituents only, one of which is a nitro, fluoro, chloro, trifluoromethyl, cyano, methoxycarbonyl, methylthio, methylsulphinyl or methanesulphonyl
 25 substituent in the para-position and the other of which is hydrogen or chloro in the meta-position.

4. An acylanilide as claimed in claim 1 wherein
 30 R^1 and R^2 , which may be the same or different, each is cyano, nitro, trifluoromethyl or chloro, R^3 and R^6 are both hydrogen, R^4 is methyl, R^5 is hydroxy and the ring A bears one substituent in the para-position which is a nitro, fluoro, trifluoromethyl, cyano, methoxycarbonyl,
 35 methylthio or methylsulphinyl substituent.

5. The compound 3,4-dichloro-(2-hydroxy-2-p-nitrophenylpropionyl)anilide;

4-nitro-3-trifluoromethyl-(2-hydroxy-2-p-nitrophenylpropionyl)aniline or

5 4-cyano-3-trifluoromethyl-(2-hydroxy-2-p-nitrophenylpropionyl)aniline.

6. The compound 3-chloro-4-nitro-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline;

3-chloro-4-methylsulphonyl-N-(2-hydroxy-2-p-nitrophenylpropionyl)aniline;

4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-trifluoromethylphenylpropionyl)aniline;

3-chloro-4-nitro-N-(2-hydroxy-2-p-trifluoromethylphenylpropionyl)aniline;

15 4-nitro-3-trifluoromethyl-N-(2-p-cyanophenyl-2-hydroxypropionyl)aniline;

4-nitro-3-trifluoromethyl-N-(2-p-fluorophenyl-2-hydroxypropionyl)aniline;

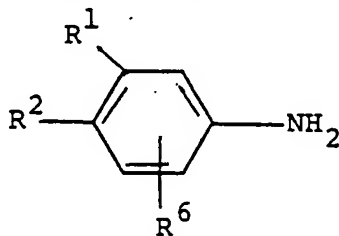
4-nitro-3-trifluoromethyl-N-(2-hydroxy-2-p-methylsulphonylphenylpropionyl)aniline;

3,4-dichloro-N-(2-hydroxy-2-p-methylsulphonylphenylpropionyl)aniline; and

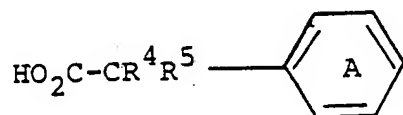
3,4-dichloro-N-(2-p-acetylphenyl-2-hydroxypropionyl)aniline.

25 7. A process for the manufacture of an acylanilide, claimed in any one of claims 1 to 6, which comprises:

(a) for the manufacture of an acylanilide wherein R^3 is hydrogen and R^5 is other than hydroxy, the reaction of an amine of the formula:-

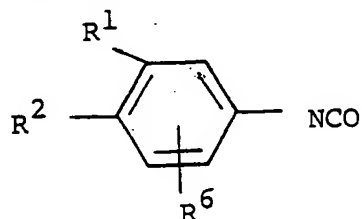


wherein R^1 , R^2 and R^6 have the meanings stated in any one of claims 1 to 4, with an acid of the formula:

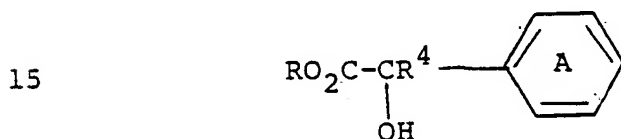


5 wherein R^4 and A have the meanings stated in any one of claims 1 to 4 and wherein R^5 is hydrogen or alkoxy or acyloxy as defined in claim 1 or 2, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein R^3 and R^5 are joined together to form carbonyl-oxy, that is, an oxazolidinedione, the reaction of an
10 isocyanate of the formula



wherein R^1 , R^2 and R^6 have the meanings stated above, with an ester of the formula



15 wherein R^4 and A have the meanings stated above and wherein R is alkyl of up to 6 carbon atoms; or

(c) for the manufacture of an acylanilide wherein R^5 is hydroxy, the hydrolysis of the corresponding
20 acylanilide wherein R^5 is acyloxy; or

(d) for the manufacture of an acylanilide wherein R^3 is hydrogen and R^5 is hydroxy, the hydrolysis of the corresponding oxazolidinedione wherein R^3 and R^5

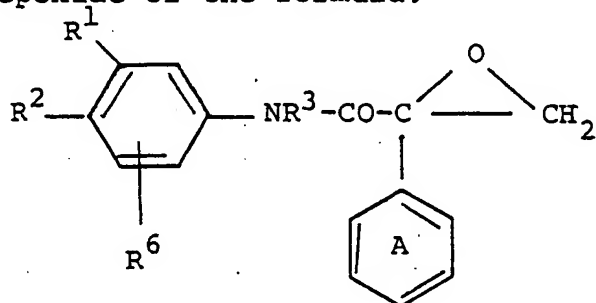
are joined together to form carbonyl-oxy; or

(e) for the manufacture of an acylanilide wherein R^3 is alkyl, the alkylation of the corresponding acylanilide wherein R^3 is hydrogen; or

5 (f) for the manufacture of an acylanilide wherein R^5 is acyloxy, the acylation of the corresponding acylanilide wherein R^5 is hydroxy; or

(g) for the manufacture of an acylanilide wherein R^3 and R^5 are joined together to form carbonyl-oxy, that is, an oxazolidinedione, the reaction of the
10 corresponding acylanilide wherein R^3 is hydrogen and R^5 is hydroxy with phosgene; or

(h) for the manufacture of an acylanilide wherein R^4 is chloromethyl and R^5 is hydroxy, the reaction of
15 an epoxide of the formula:



wherein R^1 , R^2 , R^3 , R^6 and A have the meanings stated above, with hydrogen chloride; or

(i) for the manufacture of an acylanilide wherein
20 one or more of R^1 , R^2 and a substituent in the benzene ring A is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoro-alkylsulphonyl or phenylsulphonyl, the oxidation of the corresponding acylanilide wherein one or more of
25 R^1 , R^2 and a substituent in the benzene ring A is alkylthio, perfluoroalkylthio or phenylthio, respectively; or

(j) for the manufacture of an acylanilide wherein a substituent in the benzene ring A is carboxy, the oxidation

of the corresponding acylanilide wherein a substituent in the benzene ring A is formyl; or

(k) for the manufacture of an acylanilide wherein a substituent in the benzene ring A is alkoxycarbonyl,

5 the esterification of the corresponding acylanilide wherein a substituent in the benzene ring A is carboxy.

8. A pharmaceutical or veterinary composition which comprises an acylanilide, claimed in any of claims 1 to 6, in association with a pharmaceutically
10 acceptable diluent or carrier.

9. A composition as claimed in claim 8 which additionally contains one or more drugs selected from antioestrogens, progestins, inhibitors of gonadotrophin secretion, cytotoxic agents, antibiotics and anti-
15 inflammatory agents.

10. A method of producing an antiandrogenic effect in a warm-blooded animal in need of such an effect which comprises administering to said animal an effective amount of an acylanilide claimed in any of
20 claims 1 to 6.

PH 31334

RPS/ML: 24 Apr 81



R P SLATCHER
Authorised Representative

EUROPEAN APPLICATION NO.

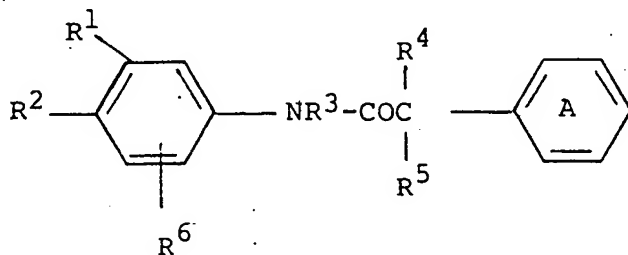
31594/CF

AMIDE DERIVATIVES, PROCESS FOR THEIR MANUFACTURE AND
PHARMACEUTICAL OR VETERINARY COMPOSITIONS CONTAINING THEM.

Claims for Austria

What we claim is:

1. A process for the manufacture of an acylanilide of the formula:-



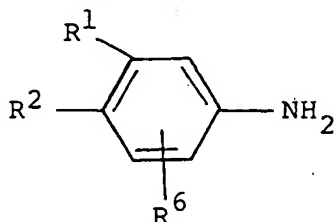
- 5 wherein R^1 is cyano, carbamoyl, nitro, fluoro, chloro, bromo, iodo or hydrogen, or alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each of up to 4 carbon atoms,
 10 or phenylthio, phenylsulphinyl or phenylsulphonyl;
 wherein R^2 is cyano, carbamoyl, nitro, fluoro, chloro, bromo or iodo, or alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl or perfluoroalkylsulphonyl each
 15 of up to 4 carbon atoms, or phenylthio, phenylsulphinyl or phenylsulphonyl;
 wherein R^3 is hydrogen or alkyl of up to 4 carbon atoms, or is joined to R^5 as stated below;
 wherein R^4 is alkyl of 2 to 4 carbon atoms, or has the
 20 formula $-CX^1X^2X^3$ wherein X^1 , X^2 and X^3 , which may be the same or different, each is hydrogen, fluorine or chlorine;
 wherein R^5 is hydrogen, hydroxy or alkoxy or acyloxy each of up to 15 carbon atoms, or is joined to R^3 to form an oxycarbonyl group such that together with the $-N-CO-C-$

part of the molecule it forms an oxazolidine-dione group;

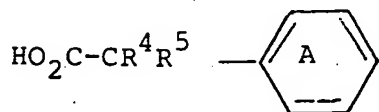
wherein R^6 is hydrogen or halogen;

and wherein the benzene ring A bears one, two or three
 5 substituents selected from hydrogen, halogen, nitro, carboxy, carbamoyl and cyano, and alkyl, alkoxy, alkanoyl, alkylthio, alkylsulphinyl, alkylsulphonyl, perfluoroalkyl, perfluoroalkylthio, perfluoroalkylsulphinyl, perfluoroalkylsulphonyl, alkoxycarbonyl and
 10 N-alkylcarbamoyl each of up to 4 carbon atoms, and phenyl, phenylthio, phenylsulphinyl and phenylsulphonyl; or bears a buta-1,3-dienylene substituent which together with the benzene ring A forms a naphthalene ring, characterised by either:-

15 (a) for the manufacture of an acylanilide wherein R^3 is hydrogen and R^5 is other than hydroxy, the reaction of an amine of the formula:-

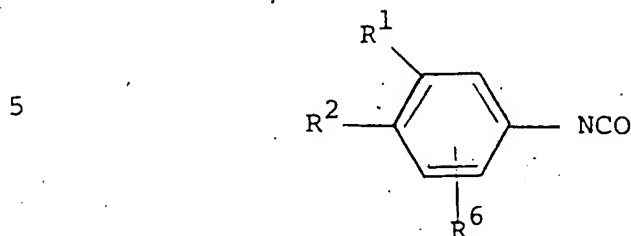


wherein R^1 , R^2 and R^6 have the meanings stated above,
 20 with an acid of the formula:-

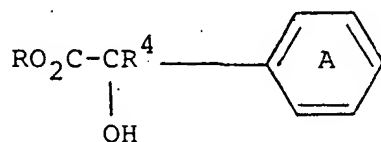


wherein R^4 and A have the meanings stated above and
 wherein R^5 is hydrogen or alkoxy or acyloxy as defined
 above, or with a reactive derivative of said acid; or

(b) for the manufacture of an acylanilide wherein R^3 and R^5 are joined together to form carbonyl-oxy, that is, an oxazolidinedione, the reaction of an isocyanate of the formula



wherein R^1 , R^2 and R^6 have the meanings stated above, with an ester of the formula



wherein R^4 and A have the meanings stated above and

10 wherein R is alkyl of up to 6 carbon atoms; or

(c) for the manufacture of an acylanilide wherein R^5 is hydroxy, the hydrolysis of the corresponding acylanilide wherein R^5 is acyloxy; or

(d) for the manufacture of an acylanilide wherein R^3 is hydrogen and R^5 is hydroxy, the hydrolysis of the corresponding oxazolidinedione wherein R^3 and R^5 are joined together to form carbonyl-oxy; or

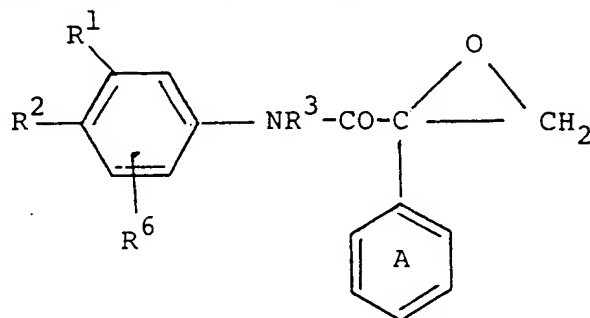
(e) for the manufacture of an acylanilide wherein R^3 is alkyl, the alkylation of the corresponding acylanilide wherein R^3 is hydrogen; or

(f) for the manufacture of an acylanilide wherein R^5 is acyloxy, the acylation of the corresponding acylanilide wherein R^5 is hydroxy; or

(g) for the manufacture of an acylanilide wherein R^3 and R^5 are joined together to form carbonyl-oxy, that is, an oxazolidinedione, the reaction of the

corresponding acylanilide wherein R^3 is hydrogen and R^5 is hydroxy with phosgene; or

- (h) for the manufacture of an acylanilide wherein R^4 is chloromethyl and R^5 is hydroxy, the reaction of
 5 an epoxide of the formula:



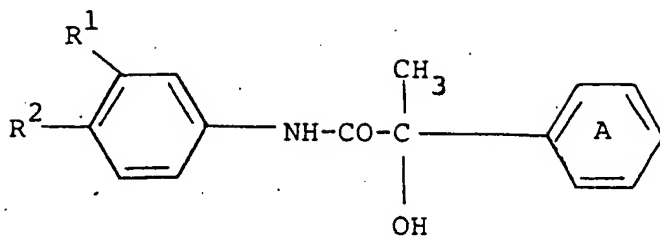
wherein R^1 , R^2 , R^3 , R^6 and A have the meanings stated above, with hydrogen chloride; or

- (i) for the manufacture of an acylanilide wherein
 10 one or more of R^1 , R^2 and a substituent in the benzene ring A is alkylsulphinyl, perfluoroalkylsulphinyl or phenylsulphinyl, or is alkylsulphonyl, perfluoroalkylsulphonyl or phenylsulphonyl, the oxidation of the corresponding acylanilide wherein one or more of
 15 R^1 , R^2 and a substituent in the benzene ring A is alkylthio, perfluoroalkylthio or phenylthio, respectively;
 or

- (j) for the manufacture of an acylanilide wherein a substituent in the benzene ring A is carboxy, the oxidation
 20 of the corresponding acylanilide wherein a substituent in the benzene ring A is formyl; or

- (k) for the manufacture of an acylanilide wherein a substituent in the benzene ring A is alkoxycarbonyl, the esterification of the corresponding acylanilide
 25 wherein a substituent in the benzene ring A is carboxy.

2. A process for the manufacture of an acylanilide of the formula:-



wherein R^1 is trifluoromethyl and R^2 is nitro or cyano;
 or R^1 is chloro and R^2 is chloro, nitro, cyano, methyl-
 thio, methylsulphinyl or methanesulphonyl; or

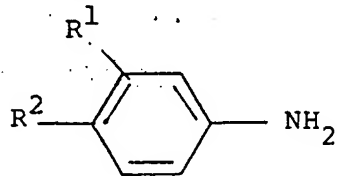
5 R^1 is cyano and R^2 is chloro; or

R^1 is nitro and R^2 is chloro or cyano; or

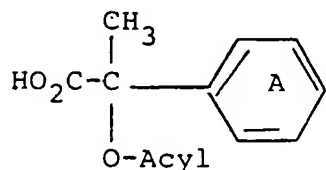
R^1 is methylthio and R^2 is cyano; or

R^1 is hydrogen and R^2 is methylthio;

and wherein the benzene ring A bears one or two
 10 substituents only, one of which is a nitro, fluoro,
 chloro, trifluoromethyl, cyano, methoxycarbonyl,
 methylthio, methylsulphinyl or methanesulphonyl
 substituent in the para-position and the other of
 which is hydrogen or chloro in the meta-position,
 15 characterised by the reaction of an amine of the
 formula:-

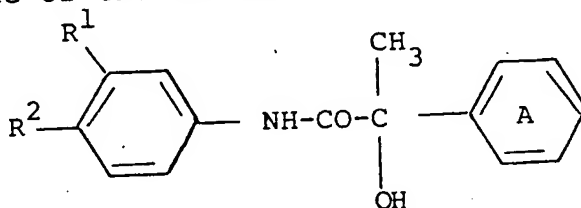


wherein R^1 and R^2 have the meanings stated above, with
 an acid of the formula:

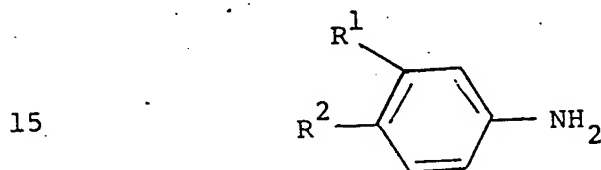


wherein A has the meaning stated above and wherein "Acyl" is acyl of up to 15 carbon atoms, or with a reactive derivative of said acid; followed by the hydrolysis of the O-Acyl group to the -OH group.

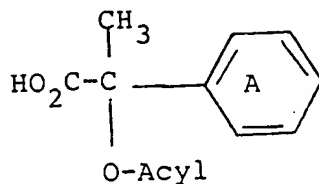
- 5 3. A process for the manufacture of an acyl-anilide of the formula:



- 10 wherein R^1 and R^2 , which may be the same or different each is cyano, nitro, trifluoromethyl or chloro, and the ring A bears one substituent in the para-position which is a nitro, fluoro, trifluoromethyl, cyano, methoxy-carbonyl, methylthio or methylsulphonyl substituent, characterised by the reaction of an amine of the formula



wherein R^1 and R^2 have the meanings stated above, with an acid of the formula:-



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- 7 -

wherein A has the meaning stated above and wherein "Acyl" is acyl of up to 15 carbon atoms, or with a reactive derivative of said acid, followed by the hydrolysis of the O-Acyl group to the -OH group.

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RPS/ML: 6 May 81



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PARTIAL EUROPEAN SEARCH REPORT
which under Rule 45 of the European Patent Convention
shall be considered, for the purposes of subsequent
proceedings, as the European search report

Application number
0040932
EP 81302147.4

DOCUMENTS CONSIDERED TO BE RELEVANT			CLASSIFICATION OF THE APPLICATION (Int. Cl.)
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	
A	GB - A - 1 113 218 (UCB) + Claims 1,33 + --	1,2,7	C 07 C 103/76 C 07 C 121/78 C 07 C 121/52 C 07 C 147/107 C 07 C 147/12 C 07 C 147/14 C 07 C 149/41 C 07 C 149/42 C 07 D 263/44 A 61 K 31/165 A 61 K 31/275 A 61 K 31/42
A	US - A - 2 721 216 (M. EUGENE SPEETER) + Examples + --	1,2,7	
	US - A - 3 995 060 (R.O. NERI, J.G. TOPLISS) + Examples 1,2; columns 17, 18 + ----	1,2,7, 8	TECHNICAL FIELDS SEARCHED (Int. Cl.) C 07 C 103/00 C 07 C 121/00 C 07 C 147/00 C 07 C 149/00 A 61 K 31/00 C 07 D 263/00
INCOMPLETE SEARCH			CATEGORY OF CITED DOCUMENTS
<p>The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims.</p> <p>Claims searched completely: 1-9 Claims searched incompletely: - Claims not searched: 10 Reason for the limitation of the search:</p> <p>Method for treatment of the human or animal body by therapy, Article 52(4) EPC</p>			<p>X: particularly relevant A: technological background O: non-written disclosure P: intermediate document T: theory or principle underlying the invention E: conflicting application D: document cited in the application L: citation for other reasons</p>
Place of search	Date of completion of the search	Examiner	
VIENNA	13-08-1981	HOFBAUER	

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